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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/619,148	07/19/2000	Kazuo Uchida	00631000049	1603

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	10

DATE MAILED: 04/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/619,148	UCHIDA ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☒ Claim(s) *1-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office Action mailed 5 July 2001 (Paper #9 filed 1/11/02) is acknowledged. In response to the amendment-B filed therein claim 1-8 were amended while claims 9-12 were canceled without prejudice. Currently, claims 1-8 are pending and under consideration.

OBJECTIONS WITHDRAWN

Priority

2. Applicant's have amended the specification to contain a specific reference to the prior application(s) – (foreign application No. 11-207913 filed 7/22/99 in Japan and foreign application No. 2000-12210 filed 1/20/00 in Japan) in the first sentence of the specification (37 CFR 1.78). Therein obviating this objection.

Information Disclosure Statement

3. Applicants acknowledge that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 has cited the references they have not been considered. The objection is withdrawn.

OBJECTIONS MAINTAINED

Oath/Declaration

4. A new oath or declaration is required because it does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The post office address should include the ZIP Code designation. The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. See MPEP §§ 602.01 and 602.02.

Applicant's new declaration is response to this objection was not received. The objection is maintained.

Drawings

5. The drawings in this application are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the examiner allows the application.

Applicant has requested deferral of the noted drawing defects until the issuance of a Notice of Allowance. However drawing correction may no longer be held in abeyance because extensions of time may no longer be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowance. Therefore Applicant is required to submit a proposed drawing correction in reply to this Office action.

REJECTIONS WITHDRAWN

Claim Rejections

6. With respect to the claim rejections under 35 U.S.C. 102 and 35 U.S.C. 103, Applicants amendments to the claims have obviated the prior art cited. The following rejections are withdrawn:

I. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Boullier et al. (Clinica Chimica Acta, 238, pages 1-10, 1995).

II. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Koren et al. (WO 96/000903).

III. Claims 2-4 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boullier et al. (Clinica Chimica Acta, 238, pages 1-10, 1995) and Koren et al. (WO 96/000903).

in view of Kaiserling et al. (Gastroenterology, 1996, Vol.110, pages 369-374) and .

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Objections

7. Claims1-8 are objected to because of the following informalities: In Claim 1, line 5 "liloprotein" should be "lipoprotein". Appropriate correction is required.

Claims 2 and 6 are objected to because of the following informalities: In Claim 2 several typos appear. For example, 2-macroglobulin should be "α2-macroglobulin". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is vague and indefinite. The preamble of the claim recites "arteriosclerosis diagnosis". However, the body of the claim is merely directed to measuring oxidized LDL with no limitations regarding diagnosis? Therein the recitation of arteriosclerosis diagnosis has no positive limitations in the claim.

B. Claims 1-8 are vague and indefinite because they are in improper Markush format. The claims utilize the phrase "is selected from", however "is selected from the group consisting of" is the appropriate phrase.

Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925). It is suggested that applicant utilize proper Markush form to clarify the claims and obviate this rejection.

C. Claims 1-8 recite "characterized in that". This is vague because the phrase is a relative phrase rendering the claims indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The phrase should be omitted. It is suggested that the claims read a method "comprising" or "consisting of" for clarity.

9. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are explained below:

The claims particularly, independent claim 1 is drawn to an assay method that employs a measuring subject complex. But the claim merely recites the detection of oxidized LDL and the detection of another substance, such claim language is not sufficient to support the method claim. The claims do not recite a binding complex between the two components therein allowing for labeling and further evaluation. How will the two components react/bind with each other to form a measurable parameter for arteriosclerosis.

An assay or method, as proposed in the preamble of claim 1 require at least a contact step between reagents and sample, the separation of unbound and bound material, a detection step, and a correlation step. These essential steps for the method have not been outlined for LDL and denatured LDL. It is suggested that Applicant add steps that at least reflect: (I) a sample and reagent contacting step, (II) the binding or complex formation of a detectable product, and (III) a correlation step. Please add appropriate steps.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Greilberger et al. (Arteriosclerosis, Thrombosis, and Vascular Biology,Vol.17, No.11, pages 2721-2728, November 1997).

Greilberger et al. teach a method of detecting the binding of oxidized-LDL labeled with Eu^{3+} and ^{125}I to tissue proteins. Microtitration plates were coated with type I collagen, type II collagen, type III collagen, type IV collagen, type V collage, fibronectin (meeting the limitation of claim 2), laminin, or poly-D-lysine were reacted with oxidized LDL. Page 2724, Binding of Oxidized. . . . The binding results were monitored via radioactivity scintillation counting and an immunological emission spectrochemical analysis (REM) of claim 5. Page 2722, 2nd column, 4th paragraph and Figure 2. The oxidized LDL was taken from human blood. See page 2722, lipoprotein preparation – LDL was isolated from the plasma of young male donors. Several additional assays were also evaluated (solid phase sandwich fluorescence, solid phase sandwich radioassay, Monvalent and Divalent Cations and Ionic Strength). The reference further teaches that the binding of LDL plays an important role in the formation of atherosclerotic lesions and arthogenesis (page 2721, 1st column, 1st paragraph).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 3-4 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greilberger et al. (Arteriosclerosis, Thrombosis, and Vascular Biology,Vol.17, No.11, pages 2721-2728, November 1997) in view of Kaiserling et al. (Gastroenterology, 1996, Vol.110, pages 369-374) .

Please see previous discussions of Greilberger et al. as set forth above.

Greilberger et al. differ from the instant invention in failing to teach the specific detection of measuring complexes involving particular blood coagulation-fibrinolytic related proteins or disinfectant substances produced by macrophages in blood cells.

However, Kaiserling et al. taught several measuring subject complexes that could be utilized in analyzing the morphology and immunophenotype of cells expressing low density lipoprotein (LDL) and oxidized LDL. See page 369, 2nd column, 4th paragraph. Numerous antibody compositions were used as possible mechanisms to determine LDL and ox-LDL in lipid cells. These antibodies include limitations found in claims 2-4, i.e alpha 1 –antitrypsin. See Table 1. Lysozyme reactivity is also discussed. See page 371, Immunohistochemical Findings.

Greilberger et al. and Kaiserling et al. are all analogous art because they are from the same field of endeavor, both inventions teach ox-LDL measurement techniques.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use various measuring subject complexes as taught by Kaiserling et al. in the method of Greilberger et al. to detect ox-LDL, because Kaiserling et al. taught that during the process of modification LDL loses its ability to bind classical LDL receptors. The modified types of LDL (oxidized and acetylated) bind one or more classes of scavenger receptors (multifunctional lipoprotein-binding receptors). See page 373, 2nd column, 3rd paragraph.

One having ordinary skill in the art would have been motivated to do this because the prior art does not contain information on all the possible complexes involving LDL and ox-LDL. Kaiserling et al. page 373, 1st paragraph, 3-4 lines. Therefore the detection of multiple complexes would render more data sets for further consideration and possible functional analysis.

With respect to the various measuring complexes outlined in the claims, these particular measuring complexes all include known compositions which are viewed as routine optimizations that are almost always determined and used in immunoassay studies.

Unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to substitute known measuring complexes in the given parameters to determine the unknown as a means of optimizing the assays provided by the art.

Response to Arguments

In response to the argument that the instant invention is not directed to antibody utility it is noted that the use of antibodies is not excluded from the claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., no antibody component) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to the argument that ~~Kaiser~~ kaiserling does not disclose the instant invention because a complex is not formed between oxidized LDL and KP-1 or KiM1p and the substance partially overlaps the reactant of applicants invention, it is noted that the claims do not require the formation of a complex but merely read on a method involving oxidized LDL and one other substance selected from an acute phase reactant, blood coagulation-fibrinolytic related proteins, or disinfectant substances produced by macrophages in blood cells.

The reference of Kaiserling et al. disclose reactants meeting the limitations of applicant's claims in table 2 (lysozyme, KP1, KiM1p, MAC387, AT, ACT, cathepsin D, UCHL1, and βF1 interactions with oxidized LDL. Page 317 .

In response to the argument that Kaiserling detects the lipid islands of human gastric mucosea while the present invention is operative with human blood, it is noted that the primary reference of Greiberger et al. teach this limitation. Kaiserling was cited to merely disclose other known blood coagulation-fibrinolytic related proteins or disinfectant substances produced by macrophages in blood cells which are involved in oxidized LDL binding. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one having ordinary skill in the art would have been motivated to do this because the prior art does not contain information on all the possible complexes involving LDL and ox-LDL. Kaiserling et al. page 373, 1st paragraph, 3-4 lines. Therefore the detection of multiple complexes would render more data sets for further consideration and possible functional analysis.

12. For reasons aforementioned, no claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 35-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
Patent Examiner
Art Unit 1641
CM1-7B17
April 19, 2002

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641